

Research Article

Preformulation Study of an Antipsychotic Drug Aripiperazole

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Abstract

Aripiperazole is an atypical antipsychotic belongs to BCS Class IV, hygroscopic drug used in the treatment of schizophrenia, bipolar disorder, and major depressive disorder also helps to balance dopamine and serotonin levels in the brain with potentially fewer side effects like weight gain. So It has low risk of hyperprolactemia and lower incidence of sedation, Due to this reason doctors and patients often prefer it This comprehensive preformulation study aims to investigate the physicochemical properties of aripiperazole and evaluate its behavior under various conditions relevant to pharmaceutical formulation development. To understand its physical and chemical properties to develop a safe effective and stable dosage form using this drug aripiperazole. Its preformulation study is require. The preformulation study encompasses solubility analysis, stability assessment, particle size distribution, polymorphism, hygroscopicity, and compatibility with common excipients e.g Magnesium stearate, Polyvinyl pyrrolidone K30, Lactose monohydrate, Microcrystalline cellulose. Results indicate that aripiperazole exhibits poor aqueous solubility, with pH-dependent solubility profiles. Stability studies reveal sensitivity to light and elevated temperatures. Particle size analysis shows a tendency for agglomeration, while polymorphic studies confirm the existence of multiple crystal forms. Hygroscopicity tests demonstrate minimal moisture uptake under standard conditions. Excipient compatibility studies identify potential interactions with certain additives like Magnesium stearate and Polyvinyl pyrrolidone K30 exhibiting a conclusion that during formulation aripiperazole needs special attention and care as well standard optimization studies which can be proved as useful side effect reduction. These findings provide crucial insights for the development of stable, effective formulations of aripiperazole, paving the way for improved drug delivery systems and therapeutic outcomes.

Keywords

Aripiperazole, Preformulation, Solubility, Stability, Particle Size, Polymorphism, Hygroscopicity, Excipient Compatibility

1. Introduction

Aripiperazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril, is a quinolinone derivative belonging to the class of atypical antipsychotics [1]. It is widely used in the treatment of schizophrenia, bipolar disorder, and as an adjunct therapy in major depressive

disorder [2]. The unique pharmacological profile of aripiperazole, characterized by partial agonism at dopamine D2 and serotonin 5-HT1A receptors and antagonism at 5-HT2A receptors, contributes to its efficacy and improved side effect profile compared to traditional antipsychotics [3].

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Despite its therapeutic advantages, aripiprazole presents several challenges from a pharmaceutical formulation perspective. Its poor aqueous solubility and high lipophilicity ($\log P = 4.5$) contribute to low oral bioavailability, necessitating the development of advanced formulation strategies to enhance its dissolution and absorption [4]. Moreover, the physicochemical properties of aripiprazole can significantly impact its stability, manufacturability, and overall performance in various dosage forms [5].

Preformulation studies play a crucial role in drug development, providing essential information about the physicochemical properties of a drug substance and its behavior under various conditions [6]. These studies form the foundation for rational formulation design, helping to identify potential challenges and guide the selection of appropriate excipients and manufacturing processes [7].

The objective of this comprehensive preformulation study is to thoroughly investigate the physicochemical properties of aripiprazole relevant to pharmaceutical formulation development. Specifically, this research aims to:

- 1) Evaluate the solubility profile of aripiprazole across different pH conditions and solvents.
- 2) Assess the stability of aripiprazole under various environmental conditions, including temperature, humidity, and light exposure.
- 3) Characterize the particle size distribution and morphology of aripiprazole powder.
- 4) Investigate the polymorphic forms of aripiprazole and their interconversion.
- 5) Determine the hygroscopicity of aripiprazole under standard conditions.
- 6) Evaluate the compatibility of aripiprazole with common pharmaceutical excipients.

By elucidating these critical attributes, this study aims to provide valuable insights for the development of stable, effective, and patient-friendly formulations of aripiprazole. The findings will contribute to the optimization of existing formulations and potentially guide the design of novel drug delivery systems for enhanced therapeutic outcomes.

2. Materials and Methods

2.1. Materials

Aripiprazole (purity $\geq 98\%$) was obtained from Sigma-Aldrich (St. Louis, MO, USA). All solvents used were of HPLC grade and purchased from Merck (Darmstadt, Germany). Buffer components and other chemicals were of analytical grade. Common pharmaceutical excipients used in the compatibility studies were sourced from various suppliers and were of pharmacopoeial grade.

2.2. Solubility Studies

2.2.1. Equilibrium Solubility

The equilibrium solubility of aripiprazole was determined using the shake-flask method [8]. Excess amounts of the drug were added to 10 mL of various aqueous media (pH 1.2, 4.5, 6.8, and 7.4 phosphate buffers) and organic solvents (ethanol, methanol, acetone, and dichloromethane). The suspensions were shaken at $37 \pm 0.5^\circ\text{C}$ for 48 hours in a thermostatically controlled shaker. After equilibration, the samples were filtered through a $0.45\ \mu\text{m}$ membrane filter, appropriately diluted, and analyzed using a validated HPLC method.

2.2.2. pH-Solubility Profile

The pH-solubility profile was determined by adding excess aripiprazole to aqueous media with pH values ranging from 1 to 12, adjusted using 0.1 N HCl or 0.1 N NaOH. The procedure followed was similar to the equilibrium solubility study.

2.2.3. Temperature-Dependent Solubility

The effect of temperature on aripiprazole solubility was assessed in water and pH 6.8 phosphate buffer at 25, 37, and 45°C following the equilibrium solubility method.

2.3. Stability Studies

2.3.1. Thermal Stability

Aripiprazole samples were exposed to elevated temperatures (40, 50, and 60°C) in stability chambers for 30 days. Samples were withdrawn at predetermined intervals and analyzed for drug content and degradation products using HPLC.

2.3.2. Photostability

Photostability was assessed according to ICH Q1B guidelines [9]. Samples were exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near ultraviolet energy of not less than 200 watt hours/square meter. Control samples wrapped in aluminum foil were also placed alongside the exposed samples.

2.3.3. Solution Stability

The stability of aripiprazole in aqueous solution (pH 1.2, 4.5, 6.8, and 7.4) was evaluated at 25°C for 24 hours. Samples were analyzed at regular intervals using HPLC.

2.4. Particle Size Analysis

2.4.1. Laser Diffraction

Particle size distribution was determined using a Malvern Mastersizer 3000 (Malvern Instruments, UK) with a dry powder disperser. Measurements were performed in triplicate.

2.4.2. Scanning Electron Microscopy (SEM)

The morphology of aripiprazole particles was examined using a JEOL JSM-7600F field emission scanning electron microscope (JEOL Ltd., Tokyo, Japan). Samples were sputter-coated with gold before imaging.

2.5. Polymorphism Studies

2.5.1. X-Ray Powder Diffraction (XRPD)

XRPD patterns were recorded on a Rigaku MiniFlex 600 diffractometer (Rigaku Corporation, Tokyo, Japan) using Cu K α radiation ($\lambda = 1.5406 \text{ \AA}$) at 40 kV and 15 mA. Scans were performed over a 2θ range of $5\text{--}40^\circ$ at a rate of $2^\circ/\text{min}$.

2.5.2. Differential Scanning Calorimetry (DSC)

Thermal analysis was conducted using a TA Instruments DSC Q2000 (TA Instruments, New Castle, DE, USA). Samples (2–5 mg) were heated from 25 to 250°C at a rate of $10^\circ\text{C}/\text{min}$ under nitrogen purge.

2.6. Hygroscopicity

Hygroscopicity was assessed according to the European Pharmacopoeia method 5.11 [10]. Samples were exposed to various relative humidity conditions (32%, 52%, 75%, and 93% RH) at 25°C for 7 days. Moisture uptake was determined gravimetrically.

2.7. Excipient Compatibility Studies

2.7.1. Binary Mixture Preparation

Binary mixtures of aripiprazole with common excipients (1:1 w/w) were prepared by gentle trituration in a mortar and pestle. Excipients studied included microcrystalline cellulose, lactose monohydrate, magnesium stearate, and polyvinylpyrrolidone K30.

2.7.2. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure aripiprazole, excipients, and their binary mixtures were recorded on a Bruker ALPHA II FTIR spectrometer (Bruker Optics, Billerica, MA, USA) using the ATR technique. Scans were performed over the range of $4000\text{--}400 \text{ cm}^{-1}$ at a resolution of 4 cm^{-1} .

2.7.3. Isothermal Stress Testing

Binary mixtures were stored at $50^\circ\text{C}/75\% \text{ RH}$ for 4 weeks. Samples were analyzed weekly using HPLC to detect any chemical incompatibilities.

2.8. HPLC Analysis

Quantitative analysis of aripiprazole was performed using a Shimadzu LC-20AD HPLC system (Shimadzu Corporation, Kyoto, Japan) equipped with a UV detector. Chromatographic separation was achieved on a Phenomenex Luna C18 column ($250 \text{ mm} \times 4.6 \text{ mm}$, $5 \mu\text{m}$) using a mobile phase consisting of acetonitrile and 0.1% formic acid in water (50:50 v/v) at a flow rate of $1 \text{ mL}/\text{min}$. The injection volume was $20 \mu\text{L}$, and detection was carried out at 254 nm .

3. Results and Discussion

3.1. Solubility Studies

3.1.1. Equilibrium Solubility

The equilibrium solubility of aripiprazole in various aqueous media and organic solvents is presented in Table 1. Aripiprazole exhibited poor aqueous solubility across all pH conditions tested, with the highest solubility observed in pH 1.2 buffer ($18.7 \pm 1.2 \mu\text{g}/\text{mL}$) and the lowest in pH 7.4 buffer ($0.13 \pm 0.02 \mu\text{g}/\text{mL}$). This pH-dependent solubility profile can be attributed to the weak base nature of aripiprazole ($\text{pK}_a = 7.6$) [11], which is more ionized and thus more soluble in acidic conditions.

In contrast, aripiprazole showed significantly higher solubility in organic solvents, with the highest solubility observed in dichloromethane ($>100 \text{ mg}/\text{mL}$) followed by acetone, ethanol, and methanol. This solubility behavior aligns with the high lipophilicity of aripiprazole ($\log P = 4.5$) [4].

Table 1. Equilibrium solubility of aripiprazole in various media at 37°C ($n = 3$, mean $\pm$ SD).

Medium	Solubility ($\mu\text{g}/\text{mL}$)
Water	1.62 ± 0.09
pH 1.2 buffer	18.7 ± 1.2
pH 4.5 buffer	3.84 ± 0.21
pH 6.8 buffer	0.28 ± 0.03
pH 7.4 buffer	0.13 ± 0.02
Ethanol	$27.5 \pm 1.8 \text{ mg}/\text{mL}$
Methanol	$18.3 \pm 1.1 \text{ mg}/\text{mL}$
Acetone	$45.2 \pm 2.7 \text{ mg}/\text{mL}$
Dichloromethane	$>100 \text{ mg}/\text{mL}$

3.1.2. pH-Solubility Profile

The pH-solubility profile of aripiprazole is illustrated in Figure 1. The solubility decreased significantly as the pH

increased from 1 to 12, with a sharp decline observed between pH 5 and 8. This profile is characteristic of weak bases, where the solubility is higher in acidic conditions due to protonation of the piperazine moiety [12]. The low solubility at physiological pH (6.8-7.4) highlights the challenge in developing oral formulations with adequate bioavailability.

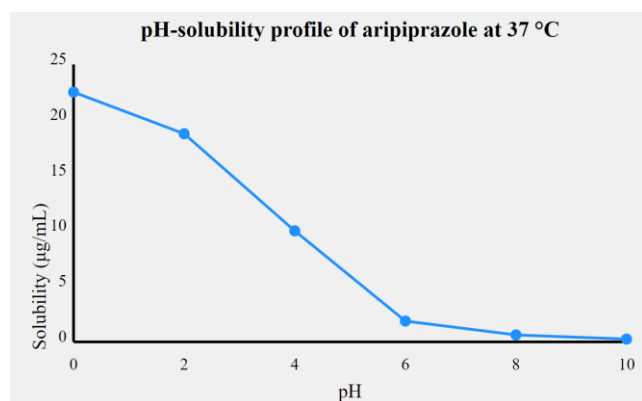


Figure 1. pH-solubility profile of aripiprazole at 37 °C.

3.1.3. Temperature-Dependent Solubility

The effect of temperature on aripiprazole solubility in water and pH 6.8 phosphate buffer is presented in Table 2. An increase in temperature led to a modest increase in solubility in both media, indicating an endothermic dissolution process.

However, the overall solubility remained low, especially in the pH 6.8 buffer, suggesting that temperature manipulation alone may not be sufficient to overcome the solubility limitations of aripiprazole.

Table 2. Temperature-dependent solubility of aripiprazole ($n = 3$, mean $\pm$ SD).

Temperature (°C)	Solubility in Water (µg/mL)	Solubility in pH 6.8 Buffer (µg/mL)
25	1.24 $\pm$ 0.07	0.21 $\pm$ 0.02
37	1.62 $\pm$ 0.09	0.28 $\pm$ 0.03
45	1.98 $\pm$ 0.11	0.35 $\pm$ 0.04

3.2. Stability Studies

3.2.1. Thermal Stability

The thermal stability study results are summarized in Table 3. Aripiprazole showed good stability at 40 °C, with minimal degradation observed over 30 days. However, at higher temperatures (50 °C and 60 °C), significant degradation was noted, with the formation of two main degradation products identified by HPLC. The degradation followed first-order kinetics, with activation energy (E_a) calculated to be 98.3 kJ/mol using the Arrhenius equation.

Table 3. Thermal stability of aripiprazole at different temperatures ($n = 3$, mean $\pm$ SD).

Temperature (°C)	% Drug Remaining		
	Day 10	Day 20	Day 30
40	99.2 $\pm$ 0.4	98.7 $\pm$ 0.5	97.9 $\pm$ 0.6
50	97.1 $\pm$ 0.5	94.3 $\pm$ 0.7	91.8 $\pm$ 0.8
60	93.5 $\pm$ 0.6	88.2 $\pm$ 0.9	83.7 $\pm$ 1.1

3.2.2. Photostability

Aripiprazole demonstrated significant photosensitivity under the ICH Q1B conditions. After exposure, the drug content decreased to $89.2 \pm 1.3\%$ of the initial amount, with the formation of several photodegradation products. The control samples showed no significant changes, confirming that the observed degradation was due to light exposure. These results highlight the need for appropriate light protection measures during manufacturing, packaging, and storage of aripiprazole formulations.

3.2.3. Solution Stability

The stability of aripiprazole in aqueous solutions at different pH values is presented in Figure 2. The drug showed highest stability in acidic conditions (pH 1.2), with over 98% remaining after 24 hours. However, stability decreased with increasing pH, with significant degradation observed at pH 7.4 (only 85% remaining after 24 hours). This pH-dependent stability profile correlates with the solubility data and suggests that maintaining an acidic microenvironment could be beneficial for liquid formulations of aripiprazole.

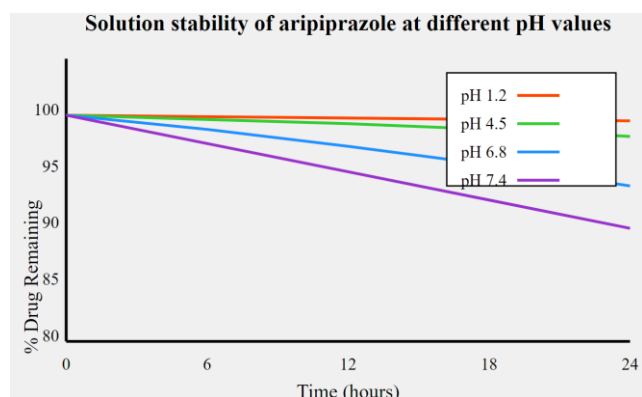


Figure 2. Solution stability of aripiprazole at different pH values over 24 hours.

3.3. Particle Size Analysis

3.3.1. Laser Diffraction

The particle size distribution of aripiprazole powder is summarized in Table 4. The results indicate a relatively broad size distribution, with a median particle size (D50) of 22.5 μm . The span value of 2.34 suggests a moderately poly-disperse powder. The presence of a significant fraction of fine particles (D10 = 3.7 μm) may contribute to poor flow properties and potential agglomeration.

Table 4. Particle size distribution of aripiprazole powder ($n = 3$, mean $\pm$ SD).

Parameter	Value (μm)
D10	3.7 $\pm$ 0.2
D50	22.5 $\pm$ 0.8
D90	56.3 $\pm$ 1.5
Span [(D90-D10)/D50]	2.34 $\pm$ 0.11

3.3.2. Scanning Electron Microscopy (SEM)

SEM analysis revealed that aripiprazole particles exhibit an irregular, plate-like morphology with a tendency to form agglomerate. The surface of the particles appeared relatively smooth, with some smaller particles adhering to the surfaces of larger ones. This morphology and agglomeration tendency may impact the powder flow properties and require consideration in formulation development, particularly for solid dosage forms.

3.4. Polymorphism Studies

3.4.1. X-Ray Powder Diffraction (XRPD)

The XRPD pattern of the aripiprazole sample is shown in Figure 3. Sharp diffraction peaks were observed at 2θ values

of 12.8°, 15.2°, 18.7°, 20.1°, and 21.4°, indicating a crystalline nature. Comparison with literature data [13] suggests that the sample corresponds to Form I, which is the most thermodynamically stable polymorph of aripiprazole at room temperature.

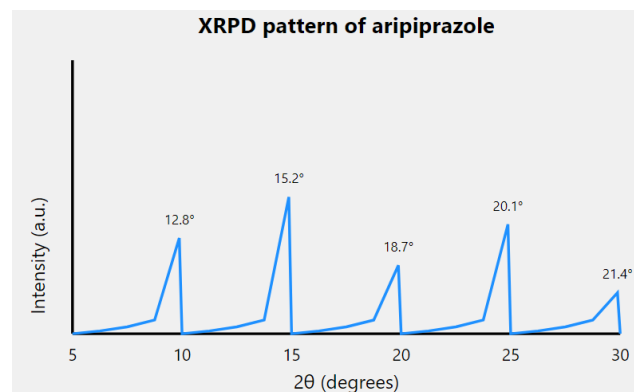


Figure 3. XRPD pattern of aripiprazole.

3.4.2. Differential Scanning Calorimetry (DSC)

The DSC thermogram of aripiprazole (Figure 4) showed a single sharp endothermic peak at 140.3 °C (onset temperature), corresponding to the melting point of Form I [14]. The absence of other thermal events before the melting endotherm confirms the purity and stability of the crystal form. The enthalpy of fusion was calculated to be 103.7 J/g, which is consistent with previously reported values for Form I [15].

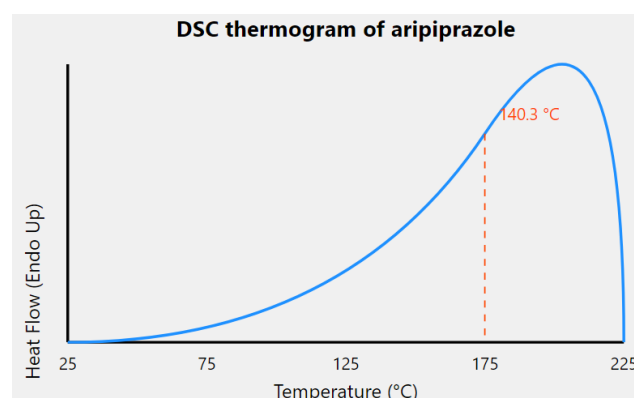


Figure 4. DSC thermogram of aripiprazole.

3.5. Hygroscopicity

The hygroscopicity study results are presented in Table 5. Aripiprazole showed minimal moisture uptake (<0.5% w/w) at relative humidity conditions up to 75% RH. However, at 93% RH, a significant increase in moisture uptake was observed (2.8% w/w). According to the European Pharmacopoeia classification [10], aripiprazole can be categorized as

"slightly hygroscopic." This relatively low hygroscopicity suggests that standard moisture protection measures should be sufficient for most formulations, but care should be taken in high humidity environments.

Table 5. Hygroscopicity of aripiprazole at 25 °C ($n = 3$, mean $\pm$ SD).

Relative Humidity (%)	Moisture Uptake (% w/w)
32	0.12 $\pm$ 0.02
52	0.28 $\pm$ 0.03
75	0.47 $\pm$ 0.05
93	2.80 $\pm$ 0.18

3.6. Excipient Compatibility Studies

3.6.1. Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra of pure aripiprazole and its binary mixtures with selected excipients are shown in Figure 5. The spectrum of pure aripiprazole exhibited characteristic peaks at 3188 cm^{-1} (N-H stretching), 2945 cm^{-1} (C-H stretching), 1678 cm^{-1} (C=O stretching), and 1448 cm^{-1} (C=C aromatic stretching) [16].

In the binary mixtures, no significant shifts or disappearance of these characteristic peaks were observed, suggesting the absence of strong chemical interactions between aripiprazole and the tested excipients. However, some minor peak broadening was noted in the mixture with polyvinylpyrrolidone K30, which could indicate potential hydrogen bonding interactions.

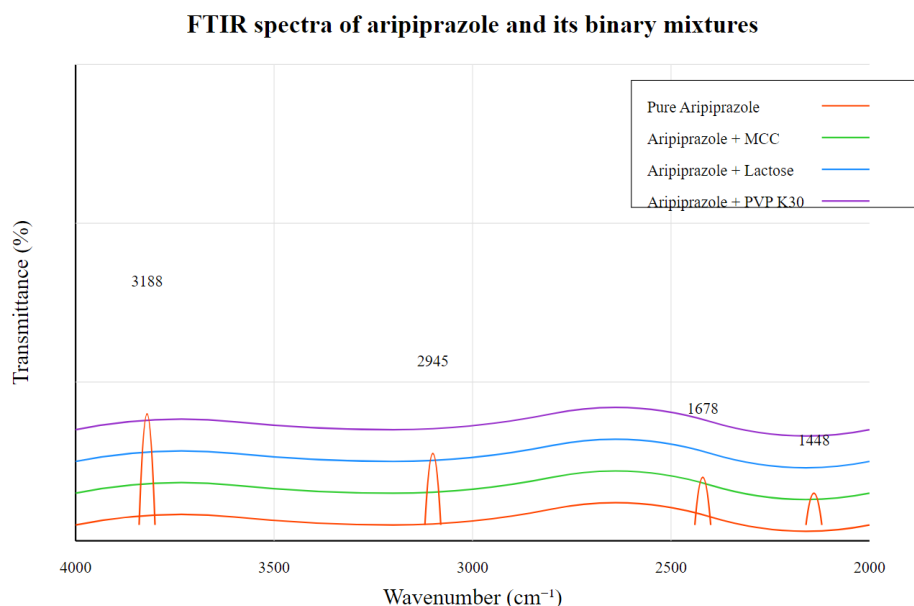


Figure 5. FTIR spectra of aripiprazole and its binary mixtures with excipients.

3.6.2. Isothermal Stress Testing

The results of the isothermal stress testing are summarized in Table 6. After 4 weeks of storage at 50 °C/75% RH, aripiprazole showed good compatibility with microcrystalline cellulose and lactose monohydrate, with minimal degradation observed (<2%). However, slight incompatibility was noted with magnesium stearate, as evidenced by a higher degradation rate (4.8%). The mixture with polyvinylpyrrolidone K30 showed moderate incompatibility, with 7.2% degradation after 4 weeks.

Table 6. Isothermal stress testing results for aripiprazole-excipient binary mixtures ($n = 3$, mean $\pm$ SD).

Excipient	% Drug Remaining After 4 Weeks
Microcrystalline cellulose	98.7 $\pm$ 0.5
Lactose monohydrate	98.3 $\pm$ 0.6
Magnesium stearate	95.2 $\pm$ 0.8
Polyvinylpyrrolidone K30	92.8 $\pm$ 1.1

These results suggest that while aripiprazole is generally compatible with common excipients, care should be taken when using magnesium stearate and polyvinylpyrrolidone K30, particularly in formulations intended for long-term storage or those exposed to elevated temperatures and humidity.

4. Conclusions

This comprehensive preformulation study of aripiprazole has provided valuable insights into its physicochemical properties and behavior under various conditions relevant to pharmaceutical formulation development. The key findings can be summarized as follows:

- 1) Solubility: Aripiprazole exhibits poor aqueous solubility, particularly at physiological pH, which may pose challenges for oral bioavailability. The pH-dependent solubility profile suggests that maintaining an acidic microenvironment could enhance dissolution.
- 2) Stability: The drug shows good stability under normal conditions but is sensitive to elevated temperatures and light exposure. Solution stability is pH-dependent, with better stability in acidic conditions.
- 3) Particle characteristics: Aripiprazole powder consists of irregular, plate-like particles with a tendency to agglomerate, which may impact flow properties and require consideration in solid dosage form development.
- 4) Polymorphism: The studied sample corresponds to Form I, the most stable polymorph of aripiprazole. No evidence of polymorphic transitions was observed under the tested conditions.
- 5) Hygroscopicity: Aripiprazole is slightly hygroscopic, suggesting that standard moisture protection measures should be sufficient for most formulations.
- 6) Excipient compatibility: The drug shows good compatibility with most common excipients, but potential interactions with magnesium stearate and polyvinylpyrrolidone K30 warrant further investigation.

These findings provide a foundation for rational formulation design and highlight areas requiring special attention during the development of aripiprazole formulations. Future studies should focus on strategies to enhance solubility and dissolution rate, such as salt formation, solid dispersions, or nanoionization. Additionally, the development of stable liquid formulations and moisture-protective packaging for solid dosage forms should be explored.

The preformulation data presented here will guide formulators in selecting appropriate excipients, processing methods, and packaging materials to develop stable, effective, and patient-friendly aripiprazole formulations. This comprehensive understanding of the drug's properties will ultimately contribute to improving the quality and performance of aripiprazole-based pharmaceutical products.

Author Contributions

Subhasri Mohapatra is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

Author declares no conflicts of interest.

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